REMARKS

Claims 19, 21-23 and 25-30 are pending. Claims 19, 28, 29 and 30 have been amended. Support for the amendments can be found throughout the application as originally filed. No new matter has been added.

Rejection Under 35 U.S.C. §112, second paragraph

Claims 19, 21, 22, 25, 27 and 30 are rejected under 35 U.S.C. §112, second paragraph, "as being indefinite foe failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention."

The Examiner asserts that claim 19 is "vague and indefinite by the phrase 'unique restriction site' as it is unclear to what the unique restriction site is related, e.g., the promoter, the immunoglobulin protein coding sequence, or the 3' noncoding sequence. In addition, each restriction site is in itself unique."

Applicants respectfully traverse this rejection. Claim 19 clearly recites that the unique restriction site is located between the promoter and the 3' non-coding sequence and that the immunoglobulin protein-coding sequence is inserted into this site. Thus, the relationship between the promoter, the restriction site, the protein-coding sequence and the 3' noncoding sequence is clear from the language in the claim.

Furthermore, with regards to the Examiner's statement that "each restriction site is in itself unique," Applicants direct the Examiner's attention to page 9, lines 19-22, which states that "[t]he vector contains 5' milk-specific promoter sequences and 3' untranslated genomic sequences that flank an XhoI cloning site. This cloning [site] is unique because it is the only one present in the vector." In view of statements such as this in the present application, it is clear the term "unique restriction site" refers to a site that is unique to the vector, and not every restriction site. Thus, Applicants respectfully request that the Examiner withdraw this rejection.

The Examiner further states that claims 19 and 28 are rendered vague and indefinite by the term "immunoglobin" as there is no previous recitation of this term in the claim."

Claims 19 and 28 have been amended, thereby obviating this rejection.

Rejections Under 35 U.S.C. §103

Claims 19, 22, 23 and 25-30 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Meade et al. (U.S. Patent Number 4,873,316, 1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076)." According to the Examiner,

> Meade et al. Disclose a DNA construct for the production of recombinant proteins comprising a milk-specific protein promoter or any promoter sequence specifically activated in mammary tissue, operably linked to a DNA sequence coding for a desired recombinant protein through a DNA sequence coding for a signal peptide that permits secretion and maturation of the desired recombinant protein in mammary tissue. ... The DNA sequence coding for the desired recombinant protein can include sequences encoding immunoglobulins ..., thus it would have been obvious to provide DNA sequence encoding heavy and/or light chains of the immunoglobulins to generate recombinant proteins in mammary tissue.
>
> Meade et al. Do not disclose a unique restriction between the promoter and the 3' non-coding sequence, wherein the immunoglobulin coding sequence is inserted into the restriction site. However, DeBoer et al. disclose a construct comprising the αSi casein promoter and 3' non-coding sequence, and unique restriction sites, including XhoI, between the promoter and the 3' non-coding sequence (see, e.g., Figures 5-7).
>
> It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the vector of Meade et al. by providing a unique restriction site, such as XhoI between the promoter and the 3' noncoding sequence as suggested by DeBoer et al. for the purpose of providing a vector which is amenable to accommodating the insertion of cDNAs encoding the protein of interest. One of ordinary skill in the art would have been motivated to provide such modified vectors to obviate any undesirable cleavage of the cDNA inserts which intrinsically contain common restriction endonuclease restriction sites.

Applicants respectfully traverse this rejection. Claims 19, 22, 23 and 25-28 are directed to DNA constructs for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal. The constructs include a promoter sequence that results in the preferential

expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence; and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the immunoglobulin protein-coding sequence is inserted into the restriction site. Claims 29 and 30 are directed to a mammary epithelial cell which includes a DNA construct as described above encoding either an immunoglobulin light or heavy chain, and a second construct encoding the opposite immunoglobulin chain (i.e., the heavy or light chain, respectively).

Meade et al. do not teach or suggest the claimed construct having a unique restriction site in between the promoter and the 3' untranslated region into which an immunoglobulin protein-encoding sequence is inserted.

Contrary to the Examiner's assertions, DeBoer et al. do not make up for the deficiencies of the Meade et al. reference. Specifically, the Examiner asserts that Figures 5-7 of the DeBoer reference demonstrate a construct having a casein promoter and a 3' non-coding sequence, and unique restriction sites, including XhoI, between the promoter and the 3' coding sequence. Applicants note, however, that none of the Figures relied upon by the Examiner demonstrate a mammary gland specific promoter and a 3' non-coding region wherein there is ***a*** unique restriction site ***into which the immunoglobulin-coding sequence has been inserted.***

As pointed out to the Examiner previously, the unique restriction site -having the coding sequence inserted into the site- allows for a vector which can easily be modified, without cleavage to the remaining construct, to insert various immunoglobulin chains. This allows for easier expression of a variety of different immunoglobulin coding sequences. Thus, the use a unique restriction site into which the immunoglobulin coding sequence is inserted, adapts to the unique features of expressing immunoglobulins. This is a feature that is not taught or suggested by either of the Meade et al. or DeBoer et al. references.

In addition, nothing in the Examiner's arguments addresses claims 29 and 30 which are directed to mammary gland epithelial cells for expressing a heterologous immunoglobulin in which the cell includes two different constructs, one for expressing the light chain and one for expressing the heavy chain. There is nothing in either the Meade et al. or DeBoer et al. which

teach or suggest expressing the light chain and heavy chain of an immunoglobulin separately by using a mammary epithelial cell comprising at least two vectors, one encoding the heavy chain and one encoding the light chain. Neither of these references even contemplates expressing these chains separately. Moreover, neither reference gives any indication whatsoever, that the use of two separate vectors can result in a cell capable of producing an assembled, functional immunoglobulin in milk. As such, these claims are clearly patentable over Meade et al. and DeBoer et al.

The Examiner further alleges that claims 19, 21-23 and 25-28 are unpatentable over Meade et al. taken with DeBoer et al., and further in view of Bischoff et al., Buhler et al., Gordon et al., and Stinnakre et al.

As discussed above, neither Meade et al. nor DeBoer et al. teach or suggest the claimed invention. Bischoff et al., Buhler et al., Gordon et al., and Stinnakre et al. are merely relied upon by the Examiner for their disclosure of specific milk protein promoters, namely whey acid promoter and lactalbumin promoter and none of these references make up for the deficiencies of Meade et al. and DeBoer et al. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

In addition, the Examiner alleges that claims 19, 22, 23, 29 and 30 are unpatentable over Meade et al. taken with DeBoer et al., and further in view of Boss et al. (U.S. Patent No. 4,816,397), Bruggemann et al. (WO 90/04306) and Weidle et al. (Gene, 98:185-191, 1991).

As discussed above, neither Meade et al. nor DeBoer et al. teach or suggest the claimed invention. None of the teachings of Boss et al., Bruggemann et al. or Weidle et al., alone or in combination, make up for the deficiencies of Meade et al. and DeBoer et al. Thus, Applicants respectfully request that the Examiner withdraw this rejection.

Obviousness Type Double Patenting

Claims 19, 20, and 22-25 are rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over claims 1, 2, and 5 of U.S. Patent No. 5,750,172.

Applicants respectfully traverse this rejection. The claims of the instant application are directed to a DNA construct for providing a heterologous immunoglobulin in the milk of a transgenic mammal. The construct includes a promoter sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence, and a unique restriction site between the promoter and the 3'non-coding sequence, wherein the immunoglobulin protein-coding sequence is inserted into the restriction site.

Unlike the instant application, the claims of U.S. Patent No. 5,750,172 do not teach or suggest the claimed construct having a unique restriction site in between the promoter and the 3' untranslated region into which an immunoglobulin protein-encoding sequence is inserted. As discussed above, the Examiner's reliance on DeBoer et al. still does not render the claimed invention as obvious. Thus, the claims of the instant application and those of U.S. Patent No. 5,750,172 are patentably distinct. Therefore, Applicants request that the Examiner withdraw this rejection.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Version with markings to show changes made

In the specification:

The following rewritten paragraph is inserted at page 1, line 2:

-- This application claims priority to U.S. Serial Number 08/170,579, now U.S. Patent Number 5,827,690, the contents of which are incorporated herein by reference.--

The paragraph at page 10, lines 5-10, has been replaced with the following rewritten paragraph:

--The 3' beta casein region begins at the PpuMI site found at Exon 7 and continues for 7.1 kb downstream. Included in this sequence are the remaining 18 kb of Exon 7, and all of Exon 8 and 9. These encode the 3' untranslated region of the goat beta casein gene, and terminate with the sequence: TAAGGTCCACAGACCGAGACCCACTCACTAGGCAACTGGTCCGTCCAGCTGTTAAGT GA (SEQ ID NO:2).--

The paragraph at page 11, lines 3-7, has been replaced with the following rewritten paragraph:

--The region immediately upstream of the initiating ATG was then mutagenized using an oligonucleotide with the following sequence: 5' AGT GAA TTC ATG CTC GAG AGC CAT GGC CTG GATC 3' (SEQ ID NO:3). Digestion of the final plasmid with XhoI produced the modified light chain cDNA that was flanked by XhoI cohesive ends.--

In the claims:

Claims 19, 28, 29 and 30 have been amended as follows:

-- 19. (Amended) A DNA construct for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal comprising a promoter sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an

[immunoglobin] immunoglobulin protein-coding sequence, a 3' non-coding sequence; and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the [immunoglobin] immunoglobulin protein-coding sequence is inserted into the restriction site.

28. (Amended) The construct of claim 19, wherein the [immunoglobin] immunoglobulin protein-coding sequence encodes a heavy chain or a fragment thereof.

29. (Amended) A mammary gland epithelial cell comprising the construct of claim 22 and a construct comprising an [immunoglobin] immunoglobulin protein-coding sequence which encodes a heavy chain or a fragment thereof, operatively linked to a promoter sequence that results in the preferential expression of the protein-coding sequence in mammary gland epithelial cells, wherein the cell expresses the light and heavy chains and secretes a heterologous, assembled immunoglobulin comprising the light and heavy chains in functional form.

30. (Amended) A mammary gland epithelial cell comprising the construct of claim 28 and a construct comprising an [immunoglobin] immunoglobulin protein-coding sequence which encodes a light chain or a fragment thereof, operatively linked to a promoter sequence that results in the preferential expression of the protein-coding sequence in mammary gland epithelial cells, wherein the cell expresses the light and heavy chains and secretes a heterologous, assembled immunoglobin comprising the light and heavy chains in functional form. --